REMARKS

Reconsideration of this application is requested in view of the amendments to the claims and the remarks presented herein.

The claims in the application are claims 17 to 28 and 41 to 47, the non-elected claims have been cancelled and are being presented in a divisional application. Claim 17 has been amended to more clearly point out the invention Portion (a) was the original claim 17 and (b) is supported on pages 5 and 6 of the application and portion (c) is supported on page 3 of the description as well as pages 2 and 8 and the examples.

Claim 17 stands rejected under 35 USC 103 as being obvious over the Celeste et al patent taken in view of the Ben-Bassat, Hirel and Georgiou taken in further view of Tonouchi and Thompson. Claims 17 and 18 stand rejected under 35 USC 103 as being obvious the same prior art taken in further view of the Hotten and Cerletti et al references. All of the claims stand rejected under 335 USC 103 as being obvious over the same rejection as claim 17 taken in further view of the Hotten and Cerletti et al references and in further view of the Neidhardt reference. The Examiner states that Examples 5 and 6 of the Celeste et al patent do not support Applicants' contention that MP52 lacks cartilage or bone formation activity because it only teaches that MP52 like BMP-12 possess tendon/ligament-like tissue inducing activity. Moreover, bone or cartilage inducing activity is not deemed to be a limitation of the claims and to argue that MP52 does not possess bone or cartilage inducing activity is to argue that the

specification does not enable the intended use. Thirdly, the Examiner is of the impression that Celeste et al BMP-12 and MP52 are clearly different proteins at the amino acid level. The Examiner is of the opinion that the Celeste et al teaches human MP52 proteins containing the amino acid sequence from Nos: 17 or 19 to No: 119 or 120 of Celeste et al's SEQ ID No: 4 and would be expected to retain activity.

Applicants respectfully traverse this ground of rejection since it is deemed that the combination of the prior art that the Examiner has made with the benefit of Applicants' teachings would not lead one skilled in the art to Applicants' invention. With respect to the Celeste et al patent, Applicants disagree with the Examiner's interpretation of Examples 5 and 6 thereof that may only teach that MP52 like BMP-12 possesses tendon/ligament-like tissue inducing activity but that they do n t support that MP52 lacks cartilage and bone inducing activity. Applicants vigorously traverse the Examiner's interpretation of these examples. In Example 5, it is explained that "No bone or cartilage formation was observed for all doses of BMP-12 tested." In contrast thereto, BMP-2 shows cartilage and bone formation as expected from the test as indicated in lines 35 to 37 of column 31. It is stated "The assay has been widely used to evaluate the bone and cartilage inducing activity of BMP's but no tendon/ligament-like tissues" (lines 22 to 24 of column 32). In Example 6, MP-52 is used within the same test system and shows "comparable results similar to those described above for human BMP-12".

This statement cannot only refer to tendon/ligaments but also must refer to the lack of cartilage/bone formation by BMP-12 and MP52. In this typical assay system,

Celeste et al could only prove "tendon/ligament-like tissue" but no cartilage or bones. If he describes this reaction which is untypical for BMP's as compared with MP-52, he could only mean that MP52 does only form tendon and ligaments. Otherwise, he would have written that also cartilage and bones are found similar to BMP-2. Such a reaction of BMP-12 should not have astonished Celeste et al since BMP-12, BMP-13 and MP52 form their own subgroup besides other BMP subgroups. If a member of the subgroup sets off in its function against other BMP's, one skilled in the art would assume that the same is also true for other members of the subgroup.

The Examiner's rejection raised under item 3 that MP-52 and BMP-12 are different proteins with regard to the amino acid level is not contradicted but because of belonging to the same subgroup, a similar behavior is rendered obvious for one skilled in the art. BMP-2 together with BMP-4 belongs to another subgroup. Applicants are submitting herewith an article by Wolfman et al wherein Celeste is also a coauthor. It can be assumed that the tests mentioned in the patent were published in this article. If the Examiner does not believe how Celeste has interpreted his results in the patent, he is referred to the article. At the end of page 321, it is clearly mentioned that GDF-5 (= MP52) would induce enchondral bone formation in the "rat ectopic bone formation assay". The authors, instead of "enchondral bone formation", only found connective tissue. It can also be seen from Table 1 that GDF-5 (MP52), GDF-6 (BMP-13) and GDF-7 (BMP-12) implants only contain tendon/ligaments whereas BMP-2, only contains bone/cartilage. Also, Figure 1 clearly shows that MP52 (GDF-5), BMP-12 (GDF-7) and BMP-13 (GDF-6) belong to their own subgroup.

Figure 1A also shows why Celeste assumes that MP52 starting with amino acid 17 (cysteine region 7 only starts at 19) could be active. BMP-12 or GDF-7 has a potential cleavage site which could result in a mature peptide containing $-NH_2$ terminal extension of only two amino acids preceding the first conserved cysteine residue (see description of the figure). His assumption of a shortened still active MP52 is probably based on the assumption of a shortened BMP-12 due to a potential alternative cleavage site with the BMP-12. This is an assumption due to another assumption and may not be generally interpreted as the Examiner has done when he states "This is evidence that one of ordinary skill in the art would expect the shortened forms to retain activity."

Under item 2, the Examiner has stated that by maintaining that MP52 does not induce the cartilage or bone, then the present application is non-enabled. This is not a correct statement since there is no question that MP52 can also induce cartilage and bones. This is proven by numerous different tests and publications which Applicants can submit to the Examiner if necessary as well as by the examples of the present application. It was only intended to make clear that Celeste et al was not able to recognize this ability of MP52 within the test conditions shown in the patent. May be, a too small dosage of MP52 or too little active MP52 was used or may be, the matrix was not optimally coated. There are many possibilities why this ability of MP52 was not discovered by Celeste.

Applicants could only find "connective tissue" in a modified "rat ectopic assay" where MP52 was applied by an ethanol precipitation whereas the same MP52 preparation lyophilized in acetonitrile/TFA has in fact, induced cartilage and bones. The dosage, method of application, duration of the test, etc. can really have an influence on the effect of MP52. Due to unspecified indications concerning influence on the effect MP52 tests in the Celeste et al patent "using methods in accordance with the above examples with minor modifications within the skill of the art", this cannot be determined. According to Applicants' tests, it is unquestioned that MP52 can induce cartilage and bones and Applicants only wanted to express that Celeste did not succeed in his test conditions to recognize the ability of MP52 to form cartilage and bones alternate to connective tissue. Celeste therefor cannot make a statement on whether shortened forms can induce cartilage or bones.

Moreover, the Examiner has indicated that the cartilage and bone inducing activity is only true for the uses according to the claims but is not limited to the protection of MP52Pro. Applicants have amended claim 17 to indicate that the MP52 must be able to induce cartilage and bones. Concerning the shortened forms, the Examiner argues that from the statement of Celeste, it can be assumed that one skilled in the art would expect the shortened forms to have activity. However, there is no support for this and Applicants are not aware of any publications concerning MP52/GDF-5 concerning any shortened forms. No publication that Applicants are aware of showed experiments for MP52 that shows it makes no difference to shorten the N-terminus and

the Examiner's statement is only an assumption and not based on knowledge. One skilled in the art generally classifies the 7-cysteine region as particularly important for the members of the TGF-β superfamily since the 7-cysteines are decisive for the three-dimensional folding (3-intramolecular cysteine bridges and an intermolecular cysteine bridge for dimer formation). This does not automatically mean that the N-terminus of the mature protein is insignificant for all members of the TGF-β family.

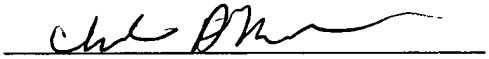
The 7-cysteine region has the highest homology within the superfamily whereas the N-terminus of the mature proteins show a considerably lower degree of homology. Applicants are submitting herewith the Ozkaynak et al reference which states on page 2091 "It is apparent that the N-terminal regions of mature TGF-β-like proteins display a striking diversity as seen with OP-1 and Vgr-1 or with BMP2a and BMP2b. The biological significance of this heterogeneity remains a challenging question." One could conclude from this that the N-terminus could be important for particular matters and that the skilled person just did not know exactly how important the N-terminus really is for individual proteins. Celeste only expresses that particular fragments should be active amino acids 17 to 19 (first, Cys of the 7 Cys region) until 119 (last Cys of the Cys region) or 120 (last amino acid). Celeste uses term "containing so it cannot automatically be assumed that all proteins which still contain these fragments are active.

The term "activity" does not reflect that the shortened protein must be comparably active like the original mature MP52. Theoretically, there could only be a remaining activity which is economically not useable. The term "will retain activity" used in the

Celeste et al patent does not indicate what activity is retained but only generally that there is an activity, no matter how much. The MP52Pro really has a comparable activity as the natural mature form of the MP52 and therefore, is an economically interesting protein. Therefore, it is deemed that the combination of the prior art does not teach Applicants' invention and withdrawal of this ground of rejection is requested.

In view of the amendments to the claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
Muserlian, Lucas and Mercanti



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Enclosures

MARKED UP VERSION OF CLAIMS SHOWING CHANGES MADE

Claim 17 (twice amended) An isolated protein consisting of the 119 amino acids as shown in SEQ ID No: 1 free of proteins of SEQ ID No: 1, with an Ala or Met and Ala at the N-terminus

(b) is expressed in E. coli using a plasmid containing DNA encoding amino acids as shown in SEQ ID No: 1 with an additional Met at its N-terminus and

(c) has a cartilage and/or bone morphogenetic activity.